

NOTES CHEMICAL & DRUG TOXICITY

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Variety of disorders caused by excessive exposure to harmful substances
- Adverse effects of exposure
 - Direct damage to DNA, disruption of metabolic processes, organ dysfunction
- Excessive exposure to offending agent
 - Intentional/unintentional, acute/chronic

SIGNS & SYMPTOMS

- See individual disorders

DIAGNOSIS

- See individual disorders

TREATMENT

MEDICATIONS

- Administer available antidote

OTHER INTERVENTIONS

- Removal of offending agent
- Address comorbidities, complications

ACUTE RADIATION SYNDROME (ARS)

osms.it/acute-radiation-syndrome

PATHOLOGY & CAUSES

- Group of organ system toxicities caused by excessive exposure to ionizing radiation of whole body/significant part of body
- Ionizing radiation
 - Composed of particles, short electromagnetic waves with potential to damage biological tissues; displaces electrons from orbits → creates unstable atoms → ionization occurs as free electrons collide with other atoms
 - Causes damage to tissues by direct impact on DNA, proteins, cell membrane lipids, generating free radicals; rapidly dividing cells most vulnerable due to

DNA damage; mutagenic, carcinogenic, teratogenic effects

Types of ionizing radiation

- X-rays, gamma rays
 - Medical, industrial, military applications (e.g. medical imaging, radiosurgery)
- Alpha particles
 - Unable to penetrate skin, harmful if ingested/inhaled (e.g. plutonium-236, uranium-238)
- Beta particles
 - Penetrate subcutaneous tissues, also harmful if ingested/inhaled (e.g. strontium-90, cesium-137)

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Measurement

- **Radiation dose:** measured in grays (Gy)
 - Amount of energy deposited into mass of tissue; 1Gy = 1 joule of absorbed energy per kilogram of biological matter
- **Effective dose:** measured in sieverts (Sv)
 - Type of radiation + variable tissue sensitivity; adjusts relative biologic effect of different radiation types on different tissues (e.g. 1Gy of alpha radiation more dangerous than 1Gy of gamma radiation)
- **Nuclear medicine procedures:** mSv; 1mSv = 1mGy
- **Typical threshold dose for whole-body/ significant partial-body irradiation**
 - $\geq 1\text{Gy}$ delivered at relatively high dose rate

Four organ-system toxicities

- **Neurovascular/cerebrovascular**
 - Caused by localized central nervous system (CNS) changes
- **Gastrointestinal (GI)**
 - Caused by loss of intestinal crypt cells, breakdown of mucosal barrier, loss of epithelium
- **Hematopoietic**
 - Caused by impairment of mitotically active hematopoietic precursors
- **Cutaneous**
 - Caused by damage to epidermis, dermis, hair follicles, subcutaneous tissues

RISK FACTORS

- Occupational exposure (e.g. medical imaging technicians)
 - Especially with insufficient shielding
- Injurious incident (e.g. nuclear power plant, transportation, overtreatment during medical therapy)
- Detonation of nuclear bomb/radiological dispersal device (dirty bomb)
- $\uparrow$ dose, rate of dose; $\downarrow$ distance from radiation source, type of radiation
- Individuals < 12 years, > 60 more sensitive to radiation

STAGING

- **Prodromal**
 - 0–2 days post-exposure; fever, tachycardia, nausea, vomiting, headache, fatigue
- **Latent phase**
 - 2–20 days post-exposure; partial functionality
- **Manifest illness**
 - 21–60 days post-exposure; progression to organ-system syndromes
- **Recovery/death**
 - Death may occur days after exposure to high amounts of radiation/ weeks, months after low exposure; death inevitable if doses $> 10\text{--}12\text{Gy}$

COMPLICATIONS

- Malnutrition, cognitive impairment, hemorrhage, permanent skin/hair loss, malignancies, infertility, congenital malformations, radiation pneumonitis, multiorgan failure, high mortality

SIGNS & SYMPTOMS

- **Neurovascular/cerebrovascular**
 - Meningeal inflammation, cerebral edema $\rightarrow \uparrow$ intracranial pressure, hemorrhage
- **GI**
 - Abdominal cramping, pain; loose stools, vomiting $\rightarrow$ fluid, electrolyte imbalance; bleeding $\rightarrow$ anemia; bowel ulceration, necrosis, perforation
- **Hematopoietic**
 - Pancytopenia; bone marrow hypoplasia, aplasia
- **Cutaneous**
 - Erythema; edema; dry, moist desquamation; ulceration (subcutaneous tissue, muscle, bone); blisters, bullae

DIAGNOSIS

DIAGNOSTIC IMAGING

CT scan

- GI
 - Segmental inflammation, bowel thickening, fibrosis, bowel obstruction
- Neurovascular/cerebrovascular
 - Cranial edema, swelling

LAB RESULTS

- Serial complete blood counts (CBCs)
 - Demonstrate changes in bone marrow function
- Peripheral blood sample
 - Cytogenetic biodosimetry analyzes chromosomal aberrations in lymphocytes; correlation with radiation dose

OTHER DIAGNOSTICS

- Geiger counter/alpha-radiation detection device
 - Determines degree of contamination
- Medical Treatment Protocols for Radiation Accident Victims (METREPOL)
 - During first 48 hours

TREATMENT

MEDICATIONS

- Nonradioactive potassium iodide (KI)
 - Take within first hours of exposure; inhibits corporation of radioactive isotopes of iodine into thyroid gland
- External decontamination
 - Wounds, body orifices

- Internal decontamination
 - Minimize absorption, maximize excretion
 - **Chelating agents:** diethylene-triamine-pentaacetic acid (DTPA)
 - **Oral ferric hexacyanoferrate (Prussian blue):** traps radioactive materials in intestines → prevents reabsorption
- Sodium bicarbonate
 - ↓ risk of renal tubular necrosis
- Pain management
- Anxiolytics

Organ-based management

- **Hematopoietic:** cytokine therapy (e.g. granulocyte colony-stimulating factor); recombinant human erythropoietin, antimicrobials
- **GI:** antiemetics (e.g. selective 5HT₃ receptor antagonists), antidiarrheals

SURGERY

Organ-based management

- **Hematopoietic:** stem cell transplant

OTHER INTERVENTIONS

- Address injuries (e.g. fractures, burns)
- Fluid, electrolyte replacement
- Lung lavage, mechanical ventilation

Organ-based management

- **Hematopoietic:** blood products
- **Neurovascular:** address increased intracranial pressure; comfort care (outcome likely fatal with neurovascular syndrome)
- **Cutaneous:** debridement, wound care

METREPOL SCORING

CRITERIA	SCORE 1	SCORE 2	SCORE 3
AVERAGE DELAY BEFORE SYMPTOMS APPEAR	< 12 hours	< 5 hours	< 30 minutes
CUTANEOUS ERYTHEMA	0	+/-	+++/before 3 hours
ASTHENIA	+	++	+++
NAUSEA	++	+++	++++
EMESIS/24 HOURS	1	1-10	> 10; intractable
TYPE, NUMBER OF STOOLS/24 HOURS	2-3; bulky	2-9; soft	> 10; watery
ABDOMINAL PAIN	Minimal	Intense	Excruciating
HEADACHE	0	+	Excruciating
TEMPERATURE	< 38°C/100°F	38–40°C/100–104°F	> 40°C/104°F
BLOOD PRESSURE	Unchanged	Unchanged/temporary ↓	Systolic blood pressure (SBP) < 80
TEMPORARY LOSS OF CONSCIOUSNESS	0	0	+/coma
DEPLETION OF LYMPHOCYTES AT 24 HOURS AT 28 HOURS	> 1,500/mcl > 1,500/mcl	< 1,500/mcl < 1,500/mcl	< 500/mcl < 100/mcl
DISPOSITION	Outpatient monitoring; survival likely	Inpatient treatment; survival possible with intensive treatment	Palliative/symptomatic treatment; survival unlikely

ARSENIC POISONING

osms.it/arsenic-poisoning

PATHOLOGY & CAUSES

- Excessive exposure (acute/chronic) to arsenic → **disruption of metabolic processes**
 - Naturally-occurring metalloid element, organic/inorganic compounds (organic—relatively low toxicity, inorganic—high toxicity)
 - Present in soil, groundwater in certain areas; in gaseous state (arsine); tasteless, odorless
- Arsenic taken up by red blood cells → distributed to all body tissues, penetrates blood-brain barrier → interacts with intracellular compounds
 - Interferes with metabolic processes (e.g. binds to sulfhydryl groups → **impairs enzymatic reactions**, interferes with **cellular respiration**)
 - Concentrates in keratin-rich tissues (e.g. skin, hair, nails)
 - Excreted in urine

RISK FACTORS

- Ingestion
 - **Contaminated groundwater**: natural leaching from soil/agricultural, industrial pollution
 - Foods (e.g. rice) grown in water containing arsenic
 - Certain Asian homeopathic compounds
- Inhalation
 - Arsenic-containing gas/dust from melting, refining, coal-fired power plants
- Occupational exposure
 - Glass manufacturing, metallurgy, mining, semiconductor manufacturing (e.g. gallium arsenide), pressure-treated wood products using chromated copper arsenate (CCA)
- Potential toxicity when administered therapeutically (e.g. arsenic trioxide for leukemia)

COMPLICATIONS

- Skin pigmentation, structural changes → squamous cell carcinoma
- Fluid, electrolyte imbalance, shock → common cause of death
- Blocks cardiac potassium channels → conduction disturbances
- Respiratory distress syndrome
- Hepatotoxicity
- Intravascular hemolysis → renal failure
- Peripheral vascular disease, gangrene (“black foot”)
- Encephalopathy
- Bone marrow depression, pancytopenia
- **Malignancies**
 - **Lung, liver**, kidney bladder, colon; **basal/squamous cell carcinoma**
- Crosses placenta → ↑ risk for spontaneous abortions, stillbirths, preterm births

SIGNS & SYMPTOMS

- GI
 - Abdominal cramping, nausea, **vomiting**, hematemesis, **diarrhea**
- Cardiovascular
 - Tachycardia, hypotension
 - **Conduction disturbances**: **QT prolongation**, ventricular dysrhythmias (e.g. torsades de pointes)
- Neurological
 - Peripheral neuropathy (“stocking-glove” distribution), diminished vibratory sensation, decreased deep tendon reflexes, delirium, seizures
- Skin
 - Plantar/palmar **hyper/hypopigmentation**, “raindrop on dusty road” pigmentation, hyperkeratosis, Mees lines on nails (transverse leukonychia)
- Breath
 - **Garlic odor**



Figure 42.1 Mee's lines appear on the nails after an episode of acute arsenic poisoning.

DIAGNOSIS

LAB RESULTS

- 24-hour urinary arsenic excretion
 - Methylated metabolites of inorganic arsenical compounds
- ↑ LFTs, hyperbilirubinemia
- CBC: anemia, leukopenia, thrombocytopenia
- ↑ blood urea nitrogen (BUN), creatinine

OTHER DIAGNOSTICS

- History of exposure, physical examination
- Analysis of hair/fingernails
 - Degree of chronic exposure

ECG

- Dysrhythmias

TREATMENT

MEDICATIONS

- Chelation therapy
 - **Dimercaprol**, AKA British anti-Lewisite (BAL); meso-2,3-dimercaptosuccinic acid (DMSA)

OTHER INTERVENTIONS

- Chronic exposure
 - Remove source, protective equipment for occupational exposure
- Fluid, electrolyte administration, correction of imbalances

CYANIDE POISONING

osms.it/cyanide-poisoning

PATHOLOGY & CAUSES

- Excessive exposure to cyanide → arrest of cellular respiration, death
 - Highly toxic chemical compound
 - Contains carbon triple-bonded to nitrogen—cyano group ($C\equiv N$)
 - Organic, inorganic, salt, liquid forms
 - **Hydrogen cyanide**: distinctive odor of bitter almonds
 - Cyanogenic compounds found in some fruit seeds (e.g. apricots, peaches)
 - Seed capsule broken, exposed to intestinal beta-glucosidase → cyanide formed
 - Also produced by certain bacteria, fungi, algae
 - **Sodium nitroprusside**: contains five cyanide groups
- Rapidly absorbed into body via all routes → 60% bound to protein → metabolized in liver → thiocyanate → eliminated via urine, lungs
- Toxic effect
 - **Blocks mitochondrial electron transport** → halts aerobic cellular respiration → cellular **hypoxia** → metabolic switch to

anaerobic pathway → lactic acidosis

RISK FACTORS

- Industrial exposure
 - Metal industries (e.g. extraction, plating), plastics, textiles
- Inhalation of smoke from burning synthetic materials
- Pediatric risk
 - Consumption of acetonitrile-containing false fingernail remover
- High rate of sodium nitroprusside administration
- Rare cases of poisoning from peach, apricot, chokecherry pits

COMPLICATIONS

- Lactic acidosis, hypoxia → cardiac failure → death

SIGNS & SYMPTOMS

- Respiratory
 - Hyperpnea, apnea, pulmonary edema; musty almond odor
- Cardiovascular
 - Hypertension (early), tachycardia, dysrhythmias, asystole
- Neurological
 - Altered level of consciousness, seizures, coma
- Mucocutaneous
 - Flushing (cherry-red), cyanosis
- Constitutional
 - Headache
- Exposure to small amounts → weakness, nausea, lacrimation, rhinorrhea

DIAGNOSIS

LAB RESULTS

- Urine cyanide, thiocyanate level
- ↓ oxygen saturation
- Arterial blood gas (ABG): lactic acidemia
- Bright red appearance of blood

OTHER DIAGNOSTICS

ECG

- Dysrhythmias

TREATMENT

OTHER INTERVENTIONS

- Remove source of exposure
- Supplemental oxygen
- Hydroxocobalamin (vitamin B_{12a})
 - Cyanokit: each hydroxocobalamin molecule binds with one cyanide ion → forms vitamin B₁₂ → excreted in urine
- Cyanide antidote kit
 - Amyl nitrate, sodium nitrate, sodium thiosulfate
 - Nitrates form methemoglobin
 - Sodium thiosulfate converts cyanide to thiocyanate → excretion in urine

ETHYLENE GLYCOL POISONING

osms.it/ethylene-glycol-poisoning

PATHOLOGY & CAUSES

- Ingestion of ethylene glycol → accumulation of toxic metabolites, metabolic acidosis, cellular dysfunction, organ damage
- Found in antifreeze, deicing solution, brake fluid, engine coolant, etc.
- Metabolism of ethylene glycol → generation of toxic metabolites
 - Ingestion → absorbed rapidly from GI system → metabolized in liver by alcohol dehydrogenase → converted into glycolaldehyde → aldehyde dehydrogenase converts glycolaldehyde to glycolic acid (later converted into oxalic acid) → metabolic acidosis
 - Concurrent ingestion of ethanol delays generation of toxic metabolites

STAGING

Stage I

- Neurologic (30 minutes–12 hours post-exposure)
 - Osmolal gap: direct effect of ethylene glycol
 - Mimics inebriation (e.g. stupor, euphoria, vomiting)
 - More severe CNS effects as ethylene glycol metabolized (e.g. nystagmus, seizures)

Stage II

- Cardiopulmonary (12–24 hours post-exposure)
 - Toxic metabolite accumulation → metabolic acidosis, oxalate crystals in heart, lungs, vasculature
 - Pulmonary edema → dyspnea; Kussmaul respirations (due to metabolic acidosis)
 - Impaired cardiac function (e.g. heart failure, circulatory collapse)

- CNS derangements (e.g. cerebral edema)
- Death likely

Stage III

- Renal (24–72 hours post-exposure)
 - Renal accumulation of calcium oxalate in kidneys + direct effects of toxic metabolites → acute tubular necrosis, renal failure

RISK FACTORS

- Ingestion of products containing ethylene glycol (unintentional/intentional)

COMPLICATIONS

- Metabolic acidosis
- Hypocalcemia, calcium oxalate crystalluria, renal failure
- Hypomagnesemia (cofactor for metabolism of glycolic acid)
- Cerebral edema, seizures, coma, death

SIGNS & SYMPTOMS

- Dizziness, headache, lethargy, slurred speech, nausea/vomiting, tachycardia, tachypnea, hyperpnea

DIAGNOSIS

LAB RESULTS

- Urinalysis: calcium oxalate crystals; hematuria; blood, protein casts
- ↑ osmolal gap (soon after ingestion) → marker for ethylene glycol
- ↑ anion gap metabolic acidosis (later) → marker for toxic metabolites
- Hypocalcemia
- ↑ BUN, creatinine
- Serum ethylene glycol
- CBC: leukocytosis

OTHER DIAGNOSTICS

- History of exposure, physical examination

ECG

- Dysrhythmias secondary to hypocalcemia

TREATMENT**MEDICATIONS**

- **Fomepizole**: inhibits alcohol dehydrogenase
- **Ethanol**: competitive inhibitor of alcohol dehydrogenase

Address acute complications

- **Fluids, sodium bicarbonate**: metabolic acidosis

- **Benzodiazepines**: seizures
- **Calcium gluconate**: hypocalcemia
- **Magnesium sulfate**: hypomagnesemia

OTHER INTERVENTIONS

- Gastric aspiration
 - Within 60 minutes of ingestion
- IV isotonic fluids → facilitate urinary excretion of metabolites
- Respiratory support
- Hemodialysis
 - Significant metabolic acidosis, renal failure, hemodynamic instability

FETAL ALCOHOL SYNDROME (FAS)

osms.it/fetal-alcohol-syndrome

PATHOLOGY & CAUSES

- Prenatal exposure to alcohol → dysmorphic craniofacial features, growth deficits, neurobehavioral impairment, CNS dysfunction
- Embryo, early fetus have underdeveloped hepatic enzymes needed for ethanol metabolism → ↓ ethanol metabolism → ↑ ethanol concentration → teratogenic effects
- Degree of alcohol-related teratogenesis influenced by stage of development, dosage, duration of exposure
 - Vulnerability continues throughout all three trimesters, all organ systems at risk

RISK FACTORS

- **Maternal alcohol consumption**
 - No safe amount of alcohol consumption during pregnancy
- Low socioeconomic status
- Poor psychological indicators
- Sibling diagnosed with FAS

COMPLICATIONS

- **Cardiac**
 - Atrial/ventricular septal **defect**
- Musculoskeletal
 - Flexion contractures, scoliosis
- Auditory
 - Conductive/neurosensory hearing loss
- Ophthalmologic
 - Optic nerve hypoplasia, strabismus
- Renal
 - Aplastic/dysplastic/hypoplastic kidneys, horseshoe kidney
- Mental health disorders
 - Attention-deficit/hyperactivity disorder, mood impairment
- Neurological
 - Seizure disorder
- **Intellectual, cognitive deficits**
- Developmental delay

SIGNS & SYMPTOMS

- Sentinel dysmorphic features
- Growth restriction (intrauterine/postnatal)
- Functional, behavioral issues
 - Poor impulse control, poor judgment, attention problems, hyperactivity; deficits in learning, speech, memory

DIAGNOSIS

OTHER DIAGNOSTICS

- Documentation of maternal alcohol consumption

Four features required

- Two of three sentinel **craniofacial anomalies**
 - **Short palpebral fissures**
 - **Smooth philtrum**
 - **Thin vermilion border of upper lip**
- **Pre/postnatal growth deficiencies**
 - Height/weight $\leq 10^{\text{th}}$ percentile (racially/ethnically-appropriate standard growth curve)
- Deficient brain growth, abnormal morphogenesis, abnormal neurophysiology, including $\geq$ one
 - Head circumference $\leq 10^{\text{th}}$ percentile
 - Structural brain anomalies visualized through imaging
 - Recurrent nonfebrile seizures (other causes of seizures ruled out)
- Neurobehavioral impairment
 - **Children $\geq$ three years old:** cognitive/behavioral impairment
 - **Children $<$ three years old:** developmental delay

TREATMENT

OTHER INTERVENTIONS

- Early intervention
 - Occupational, speech, behavioral therapy; specialized education; parenting training

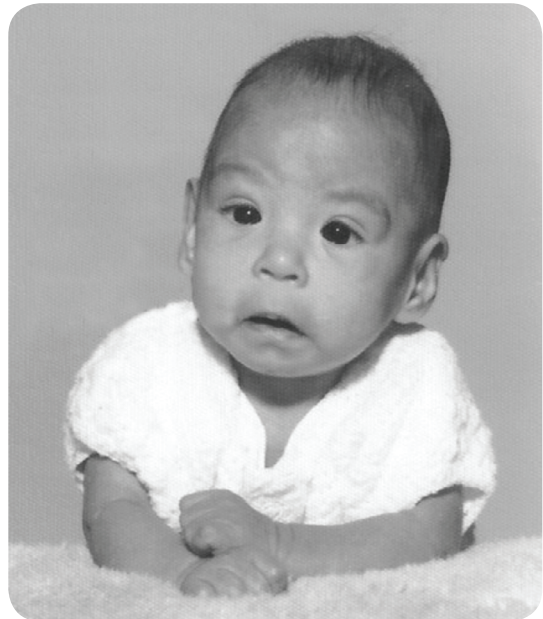


Figure 42.2 The face of a baby diagnosed with fetal alcohol syndrome. There is a smooth philtrum, a thin upper lip and small eye openings.

FETAL HYDANTOIN SYNDROME

osms.it/fetal-hydantoin-syndrome

PATHOLOGY & CAUSES

- Prenatal exposure to phenytoin/metabolites → spectrum of congenital anomalies, growth deficiencies
- Teratogenic mechanism unclear; may be related to phenytoin-associated impairment of folate absorption

RISK FACTORS

- Prenatal exposure to phenytoin/metabolites; no safe amount of phenytoin during pregnancy

COMPLICATIONS

- Microcephaly, congenital heart defects, growth deficiency, systemic abnormalities (e.g. nervous, renal, GI systems)

SIGNS & SYMPTOMS

- Craniofacial anomalies
 - Wide anterior fontanel; ocular hypertelorism, epicanthal folds; nasal (short; flat, broad nasal bridge); mouth

(bowed upper lip; broad alveolar ridge; cleft lip, palate)

- Limbs
 - Stiff, tapered fingers; digit, nail hypoplasia; hip dislocation
- Mild/moderate growth deficiencies
 - Prenatal onset, continues through postnatal life
- Mild/moderate mental deficiencies
- Short neck, umbilical/inguinal hernia, pilonidal sinus, low-set hairline

DIAGNOSIS

OTHER DIAGNOSTICS

- History of maternal ingestion of phenytoin during pregnancy, physical examination

TREATMENT

OTHER INTERVENTIONS

- Early intervention
 - Occupational, speech, behavioral therapy; specialized education

MERCURY POISONING

osms.it/mercury-poisoning

PATHOLOGY & CAUSES

- Excessive exposure to mercury → neurotoxicity, widespread interruption of cellular processes, teratogenesis
- Naturally occurring metal found in various forms in environment
 - Organic, inorganic, methylmercury (MeHg)

Sources

- Medical preservative (thiomersal)
- Thermometers (phased out)
- Dental amalgam
- Dietary: inorganic mercury from industrial waste → transformed to methylmercury by soil, marine organisms → bio-amplified in tissues of predatory fish (e.g. tuna)
- Household items (e.g. fluorescent bulbs,

- batteries, paint)
- Fungicides, pesticides
- Some homeopathic folk remedies

Properties

- Lipid soluble; easily crosses cellular membranes
 - Disrupts cellular physiology by binding to functional groups (e.g. sulfhydryl, carboxyl, phosphoryl)
 - Crosses blood-brain barrier → neurotoxic effects (impairs synthesis of proteins, nucleic acids; disrupts neurotransmitter synthesis, uptake)
 - Crosses placenta → concentrates in fetus → teratogenic effects
- High affinity for sulfhydryl groups in red blood cells (RBCs) → distributed throughout body
- Other organ toxicities
 - Concentrates in kidneys → oxidative damage; pulmonary, GI
- Eliminated in feces, urine

RISK FACTORS

- Occupational (e.g. dentists, hygienists, miners, ceramic workers, taxidermy)

COMPLICATIONS

- Minamata disease
 - Neurotoxicity caused by severe methylmercury poisoning
- Renal, respiratory failure; hemorrhagic colitis; fetal anomalies, death

SIGNS & SYMPTOMS

- Acute exposure
 - Cough, dyspnea, circulatory collapse, vomiting, bloody diarrhea
- Chronic inhalation exposure (classic triad)
 - Tremor (e.g. intentional tremor, tetanus mercurialis)

- Neuropsychiatric problems (e.g. fatigue, memory loss, mental instability)
- Gingivostomatitis
- Chronic ingestion exposure
 - **Nervous system:** tremor, headache, dysarthria, paresthesia, irritability, psychosis
 - **Cardiovascular:** hypo/hypertension
 - **Hematologic:** cytopenias
 - **Ocular:** conjunctivitis; corneal opacities, ulcers

DIAGNOSIS

LAB RESULTS

- Mercury, anemia in urine/blood; leukocytosis
- Renal tubular damage
 - N-acetyl-beta-D-glucosaminidase (NAG), albuminuria, epithelial cell casts, oliguria

TREATMENT

MEDICATIONS

- **Chelation therapy:** oral DMSA, intravenous (IV) **dimercaprol** (contraindicated with methylmercury, may shift mercury to brain)

OTHER INTERVENTIONS

- Remove source of exposure; IV fluids, electrolytes; respiratory support

PARACETAMOL TOXICITY

osms.it/paracetamol-toxicity

PATHOLOGY & CAUSES

- Excessive ingestion of paracetamol (acetaminophen) → fulminant hepatic failure, coma, death
- Acetaminophen metabolism in liver
 - 90% conjugated via glucuronic acid → nontoxic compounds → excreted in urine
 - 2% excreted unchanged in urine
 - Remainder metabolized by cytochrome P450 system → toxic intermediary N-acetyl-p-benzoquinone imine (NAPQI) conjugated by hepatic glutathione → further metabolized → excreted in urine
 - Glutathione rapidly depleted in acute overdose → accumulation NAPQI → binds to cellular proteins → hepatic necrosis
- Multiple acetaminophen-containing products, acetaminophen
- Concomitant ingestion of certain drugs
 - Hepatic enzyme inducers (e.g. CYP2E1 inducers isoniazid, rifampin, phenobarbital), drugs that deplete glutathione (e.g. zidovudine, trimethoprim-sulfamethoxazole)
- Decreased hepatic glucuronidation capacity (e.g. chronic alcohol use)
- Existing hepatic disease (e.g. alcoholic liver disease, hepatitis)
- Genetic
 - Gilbert syndrome (inherited deficiency in glucuronidation), cytochrome P450 polymorphisms

COMPLICATIONS

- Liver failure; death related to liver, multiorgan failure

STAGING

Stage I

- 0–24 hours post-ingestion; nonspecific indications of toxicity

Stage II

- 24–72 hours post-ingestion; onset of hepatotoxicity, deterioration of renal function

Stage III

- 72–96 hours post-ingestion; fulminant hepatic failure

Stage IV

- hepatic recovery; regeneration of liver if individual survives Stage III

RISK FACTORS

- Acute overdose of acetaminophen (intentional/unintentional)
- Chronic ingestion of supratherapeutic doses

SIGNS & SYMPTOMS

- May be asymptomatic/demonstrate nonspecific findings (e.g. nausea, vomiting, malaise)
- Progressive liver damage
 - Right upper quadrant (RUQ) pain, jaundice, hypoglycemia, coagulopathy, hepatic encephalopathy, impaired renal function, metabolic acidosis

DIAGNOSIS

LAB RESULTS

- **Urinalysis:** renal damage
- Serial blood draws for serum acetaminophen concentration
 - Plot on the Rumack–Matthew nomogram if time of ingestion known
- LFTs
 - ↑ **transaminases:** AST, ALT

- ↑ bilirubin, lipase
- Metabolic panel
 - ↑ BUN, creatinine, ammonia; ↓ glucose
- Coagulation
 - ↓ prothrombin time, INR
- ABG
 - ↓ pH; anion gap

OTHER DIAGNOSTICS

- History of acetaminophen use, physical examination (liver toxicity)

TREATMENT

MEDICATIONS

- **Acetylcysteine**: most effective if administered within eight hours of ingestion; replenishes glutathione, detoxifies NAPQI

SURGERY

- Liver transplant

OTHER INTERVENTIONS

- **Activated charcoal**: adjunctive treatment for GI decontamination
- Address complications
 - **Hemodialysis**: renal failure
 - **Fresh frozen plasma**: coagulopathy

SEROTONIN SYNDROME

osms.it/serotonin-syndrome

PATHOLOGY & CAUSES

- Potentially life-threatening disorder
 - **Excessive** presence of serotonin (5-hydroxytryptamine/5-HT), overactivation of central serotonin receptors → clinical manifestations related to mental status, neuromuscular excitation, autonomic excitation
- May be caused by therapeutic use of single serotonergic drug, overdose, drug interactions between ≥ two drugs

5HT increase

- ↑ serotonin synthesis
 - Phentermine, L-tryptophan
- ↑ serotonin release
 - Amphetamines/amphetamine derivatives; dopamine agonists
- ↑ activation of serotonergic receptors
 - Certain antidepressants (buspirone); triptans; prokinetic agents (e.g.

metoclopramide); ergot alkaloid derivatives; lithium

- ↓ serotonin reuptake
 - **Selective serotonin reuptake inhibitors** (SSRIs); **serotonin noradrenergic reuptake inhibitors** (SNRIs); **tricyclic antidepressants** (TCAs); 5HT₃ receptor antagonists; certain opiates (e.g. methadone, **tramadol**), drug abuse (e.g. **ecstasy**); **Saint John's wort**
- ↓ serotonin metabolism
 - **Monoamine oxidase inhibitors** (MAOIs); **triptans**
- ↓ activity of certain CYP450 enzymes
 - **Dextromethorphan**

RISK FACTORS

- Therapeutic use of serotonergic drug
- Polypharmacy (increases likelihood of drug interaction)

COMPLICATIONS

- Ventricular dysrhythmias
- Rhabdomyolysis, myoglobinuria (due to hyperthermia) → renal failure
- Metabolic acidosis
- Acute respiratory distress syndrome

SIGNS & SYMPTOMS

- Neuromuscular excitation
 - Hyperreflexia, tremors, clonus, muscle rigidity, bilateral Babinski sign
- Autonomic nervous system hyperactivity
 - Vomiting, diarrhea, hypertension, tachycardia, dysrhythmias, tachypnea, diaphoresis, hyperthermia, mydriasis
- Altered mental status
 - Anxiety, agitation, confusion

DIAGNOSIS

LAB RESULTS

- ↑ white blood cell count, creatine phosphokinase; ↓ serum bicarbonate

OTHER DIAGNOSTICS

Hunter Serotonin Toxicity Criteria

- History of taking serotonergic agent + any one of following clinical features
 - Spontaneous clonus
 - Inducible clonus + agitation/diaphoresis
 - Ocular clonus + agitation/diaphoresis
 - Tremor + hyperreflexia
 - Hypertonia + temperature > 38°C/100°F + ocular/inducible clonus

TREATMENT

MEDICATIONS

- Antidote (if supportive measures insufficient)
 - Cyproheptadine (H1, 5-HT2 antagonist effects)
- Benzodiazepines, short-acting antihypertensives
 - Address symptomatology

OTHER INTERVENTIONS

- Discontinue serotonergic drug
- Cooling measures, IV fluids, supplemental oxygen
 - Address symptomatology